REMARKS

The specification has been amended to delete references to certain web sites, and the claims have been amended to clarify the invention. Specifically, claims 1 and 4 have been amended to delete the recitation of non-elected inventions. Claim 3 has been amended to delete "a biologically active portion of SEQ ID NO:2" and to recite a specific antigenic epitope of SEQ ID NO:2 "from about amino acid residue K189 to about amino acid residue Q236 of SEQ ID NO:2". Support for the amendment to claim 3 is found in the specification at p. 11, line 9, which recites the specific epitope of ARP-2 (SEQ ID NO:2). No new matter is added by these amendments and entry of the amendments is therefore requested.

Objection to the Disclosure

The Examiner has objected to the disclosure as it refers to embedded hyperlinks and/or other forms of browser-executable code which are impermissible and require deletion. See MPEP § 608.01.

Applicants point out that the MPEP § 608.01 states that this policy is based on the principle that "USPTO policy does not permit the USPTO to link to any commercial sites since the USPTO exercises no control over the organization, views or accuracy of the information contained on those outside sites (underline added). Section 608.01 goes on to state that "where hyperlinks and/or other forms of browser-executable codes are a part of the applicant's invention and it is necessary to have them included in the patent application in order to comply with the requirements of 35 U.S.C. 112, first paragraph, and applicant does not intend to have these hyperlinks as active links, examiners should not object to these hyperlinks. The Office will disable these hyperlinks when preparing the text to be loaded onto the USPTO web database (underline added). The web site recited at p. 31, line 5 is a non-commercial, government web site specifically associated with the National Center for Biotechnology Information (NCBI). In addition, Applicants further declare that the web site cited at p. 31, as well as the one cited at p. 33, is not intended as an active hyperlink but is recited to identify the specific source of the software algorithms used for purposes of enablement, and that the recitation in the application therefore complies with the requirements of the MPEP § 608.01. However, in the interest of expediting prosecution and the allowance of claims, the recited web sites have been deleted. Withdrawal of the objection is therefore requested.

Objection to Claims 1 and 3-8

The Examiner has objected to claims 1 and 3-8 as being drawn in the alternative to the subject matter of non-elected claims. Non-elected subject matter has been deleted from the claims, and withdrawal of the objection is therefore requested.

35 U.S.C. 112, First Paragraph, Rejection of Claims 1 and 3-8

The Examiner has rejected claims 1 and 3-8 under 35 U.S.C. § 112, first paragraph, as containing subject matter which is not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Examiner stated that the claims are drawn to a cDNA, which the specification defines on page 7. According to the definition provided, the claims encompass a genomic cDNA molecule encoding a protein having the amino acid sequence of SEQ ID NO:2 or a variant thereof having an amino acid sequence that is at least 95% identical to SEQ ID NO:2. Furthermore, the claims are drawn to a naturally occurring variant of SEQ ID NO:2.

The Examiner stated that the specification describes a consensus polynucleotide sequence derived from a group of putatively overlapping DNA molecules that were synthesized using different messenger RNA molecules or fragments thereof as templates. However, the Examiner stated, the specification does not include a detailed description of a genomic DNA isolate that encodes SEQ ID NO:2 nor does it appear to describe any nucleic acid molecule encoding a variant of SEQ ID NO:2 having an amino acid sequence that is at least 95% identical to SEQ ID NO:2. Moreover, while on page 9 the specification defines "variant" as "recognized variants of a cDNA", it is noted that the specification fails to describe features that are common to at least a substantial number of members of the claimed genus of cDNA molecules.

Applicants response

Applicants disagree that the claims encompass a genomic DNA encoding SEQ ID NO:2 or a variant of that sequence. Applicants further disagree that such variants as are claimed are not sufficiently described in the specification that one skilled in the art would not recognize applicants possession of them.

The definition of cDNA referred to by the Examiner at p. 7 of the specification reads as follows:

> "cDNA" refers to an isolated polynucleotide, nucleic acid molecule, or any fragment or complement thereof. It may have originated recombinantly or synthetically, be double-stranded or single-stranded, represent coding and/or noncoding 5' and 3' sequence.

The definition given does contradict in any way the well known fact in the art that a cDNA is always derived from messenger RNA (mRNA) that is itself derived entirely from exons of genomic DNA and cannot contain introns of genomic DNA. A cDNA derived from such mRNA could also not encompass a

genomic DNA. Therefore the claims cannot be construed as encompassing genomic DNA, and one skilled in the art would clearly recognize this to be so.

With regard to the definition of "variants" referred to by the Examiner at p. 9, the definition goes on to recite a number of specific parameters that define "recognized variations of a cDNA", including BLAST score, allelic variants, and single nucleotide polymorphisms. The specification further describes specific features common to AISP-related proteins, including ARP-2, at p. 11, lines 2-11. In particular, conserved PDZ domains and the aPCK binding region characteristic of the family of proteins are described. See also BACKGROUND OF THE INVENTION at top of p. 2. Given SEQ ID NO:2, together with these specific structural and functional features, one skilled in the art would clearly understand applicants possession of polynucleotides encoding a variant of SEQ ID NO:2 having at least 95% sequence identity to SEQ ID NO:2. Applicants further believe such description is in compliance with the law as it has been applied to 35 U.S.C. § 112, first paragraph.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics[42] which provide evidence that applicant was in possession of the claimed invention,[43] i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.[44] What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.[45] If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.[46]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

SEQ ID NO:2 is specifically disclosed in the application (see, for example, page 3, lines 4-6). Variants of SEQ ID NO:2 having at least 95% identity to SEQ ID NO:2 are described, for example, at

page 3, lines 6-7. Incyte clones in which the nucleic acids encoding the human ARP-2 were first identified and libraries from which those clones were isolated are described, for example, at page 10, lines 12-22 of the Specification. Chemical and structural features of ARP-2 are described, for example, on page 10, line 23 through page 11, line 8. Given SEQ ID NO:2, one of ordinary skill in the art would recognize naturally-occurring variants of SEQ ID NO:2 having at least 95% sequence identity to SEQ ID NO:2. Accordingly, the Specification provides an adequate written description of the recited polypeptide sequences.

A. The Specification provides an adequate written description of the claimed "variants" of SEQ ID NO:2.

The Office Action has asserted that the claims are not supported by an adequate written description because

> the specification does describe any nucleic acid molecule encoding a variant of the polypeptide of SEQ ID NO:2 having an amino acid sequence that is at least 95% identical to SEQ ID NO:2
>
> (page 5 of the Office Action)

Such a position is believed to present a misapplication of the law.

1. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written

> description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. §112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polynucleotides or polypeptides in terms of chemical structure, rather than on functional characteristics. For example, the "variant language" of independent claim 1 recites chemical structure to define the claimed genus:

> 1. An isolated cDNA, or the complement thereof, encoding a protein having the amino acid sequence of SEQ ID NO:2, or a naturally occurring variant of SEQ ID NO:2 having at least 95% amino acid identity to SEQ ID NO:2.

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:2. In the present case, there is no reliance merely on a description of functional characteristics of the polynucleotides recited by the claims. In fact, there is no recitation of functional characteristics. Moreover, if such functional recitations were included, it would add

to the structural characterization of the recited polynucleotides. The polynucleotides defined in the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base its written description inquiry "on whatever is now claimed," the Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*

2. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant." Available evidence illustrates that the claimed genus is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the enclosed reference (Exhibit A) by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.). See also p. 31, lines 11-14 of the specification.

The present application is directed, *inter alia*, to ASIP proteins related to the amino acid sequence of SEQ ID NO:2. In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as ASIP proteins and which have as little as 40% identity over at least 70 residues to SEQ ID NO:2. The "variant language" of the present claims recites, for example, polynucleotides encoding "a naturally-occurring amino acid sequence having at least 95% sequence identity to the sequence of SEQ ID NO:2" (note that SEQ ID NO:2 has 1356 amino acid residues). This variation is far less than that of all potential ASIP proteins related to SEQ ID NO:2, i.e., those ASIP proteins having as little as 40% identity over at least 70 residues to SEQ ID NO:2.

3. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. §112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023

filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those case was based on the state of the art at essentially at the "dark ages" of recombinant DNA technology.

The present application was filed in January 2001. Much has happened in the development of recombinant DNA technology in the 20 or more years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances one of skill in the art would recognize that, given the sequence information of SEQ ID NO:2, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polynucleotide variants at the time of filing of this application.

For all of the above reasons, applicants submit that they are in possession of the claimed invention, at least as recited in claims 1 and 3-8 and therefore request withdrawal of the rejection of claims under 35 U.S.C. § 112, first paragraph.

35 U.S.C. § 112, First Paragraph, Rejection of Claims 1 and 4-8

The Examiner has rejected claims 1 and 4-8 under 35 U.S.C. § 112, first paragraph, as containing subject matter which is not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Examiner stated that claims 1 and 4 recite a "naturally occurring variant". However, there does not appear to be proper and sufficient antecedent basis in the specification for the recitation of these terms. Therefore the recitation of the terms in the claims appears to introduce new matter. Applicants were invited to point to specific disclosures in the specification that are believed to provide the necessary support for these terms.

The terms "naturally occurring" are used throughout the specification, in addition to being well understood in the art. For example, at page 7, line 13, "naturally occurring molecules"; at page 12, line 41, "naturally occurring gene"; and at page 13, line 2, "naturally occurring ARP". Thus, there is ample support in the specification for the use of the terms. Withdrawal of the rejection of claims 1 and 4-8 under 35 U.S.C. § 112, first paragraph is therefore requested.

35 U.S.C. § 112, Second Paragraph, Rejection of Claims 1 and 3-8

The Examiner has rejected claims 1, 3 and 5-8 under 35 U.S.C.§ 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) The Examiner stated that claims 1, 3 and 5-8 are vague and indefinite because claims 1 and 3 recite the term "isolated cDNA...encoding a protein". At page 7, the specification defines the term "a cDNA encoding a protein" as a nucleic acid sequence that closely aligns with sequence which encode conserved regions, motifs or domains that were identified by employing analyses well known in the art. Therefore, the Examiner stated, it is unclear how closely the claim requires the claimed nucleic acid sequence to align with sequences that encode conserved regions, motifs of a protein having the amino acid sequences set forth in SEQ ID NO:2 or a naturally occurring variant thereof. Accordingly, one of ordinary skill in the art would not be reasonably appraised of the metes and bounds of the invention.

The definition of "cDNA encoding a protein" referred to by the Examiner at page 7 of the specification defines the phrase in its broadest context in the absence of any other limitations. Claim 1 clearly recites a "...cDNA....encoding a protein having the amino acid sequence of SEQ ID NO:2, or a naturally occurring variant of SEQ ID NO:2 having at least 95% amino acid identity to SEQ ID NO:2". Likewise claim 3 recites a"...cDNA...encoding a protein having the amino acid sequence of SEQ ID NO:2, or an antigenic epitope of SEQ ID NO:2 from about amino acid residue K189 to about amino acid residue Q236 of SEQ ID NO:2". Thus the "cDNA encoding a protein" in these claims is further limited to the amino acid sequence of SEQ ID NO:2, a variant having at least 95% sequence identity to SEQ ID NO:2, and a specified antigenic epitope of SEQ ID NO:2. In addition to the sequence of SEQ ID NO:2 itself, a variant having at least 95% sequence identity to SEQ ID NO:2 is defined, as discussed previously in this response, by SEQ ID NO:2 and specific structural features shared by SEQ ID NO:2 and related proteins at pp. 10-11 of the specification. The specific claimed antigenic epitope of SEQ ID NO:2 is disclosed at p. 11, line 9 of the specification. Thus the metes and bounds of the proteins encoded by the cDNAs in the claims are clearly defined beyond the broader definition of what may constitute a "cDNA encoding a protein" given in the specification.

(b) The Examiner stated that claim 3 is vague and indefinite because of the recitation of the term "biologically active portion of SEQ ID NO:2". The Examiner stated that the term is vague and indefinite because any and all biological materials, e.g., a carboxyl group, which is indeed a portion of material represented by SEQ ID NO:2, are biologically active in many regards.

As noted above, the specification specifically recites "biologically active portions of ARP-2" (SEQ ID NO:2) at p. 11, lines 10-11 that encompass significant biological activities such as PDZ domains involved in protein-protein interactions (see p. 2, lines 1-2), and the aPCK binding domain of ASIP proteins. One skilled in the art would clearly not ascribe such a vague and broad definition to the term as suggested by the Examiner based on these specific disclosures by applicant. However, for reasons given below, the term "biologically active portions" have been deleted from the claim.

(c) The Examiner stated that claim 4 is indefinite because it is unclear whether the claim requires the cDNA to consist of or comprise a nucleic acid sequence of SEQ ID :20 or the complement thereof to consist of or comprise a fragment of SEQ ID NO:20 selected from the group consisting of---.

Applicants submit that the phrase "selected from" is generally interpreted in its broadest sense to mean "comprising". However, claim 4 has been amended to recite a cDNA "comprising a sequence" selected from---, and at step b) to recite "a fragment of SEQ ID NO:20 consisting of SEQ ID NO:21". The claim, as amended, is therefore clear and definite.

(d) The Examiner stated that claim 8 is indefinite because the claim recites "using a cDNA to produce a protein". The claim does not clearly delineate the metes and bound of the invention because it cannot be determined whether the protein to which the phrase refers is the protein encoded by the cDNA molecule of claim 1 or any cDNA molecule of which the cell is comprised.

Since the host cell of claim 7 comprises the expression vector of claim 6, and said vector comprises only the cDNA of claim 1, clearly the method of claim 8 can only be used to produce a protein described in claim 1 and not just "any cDNA molecule of which the cell is comprised" as suggested by the Examiner. One skilled in the art would clearly recognize this fact, particularly in view of applicants disclosure of the recombinant protein expression process as described at pp. 16-17 of the specification.

With the above amendments and remarks, applicants believe that claims 1 and 4-8 are clear and definite and therefore request withdrawal of the rejection of claims under 35 U.S.C.§ 112, second paragraph.

35 U.S.C. § 102(a), Rejection of Claims 3 and 4

The Examiner has rejected claims 3 and 4 under 35 U.S.C. § 102(a) as being anticipated by Joberty et al. (2000). The Examiner stated that Joberty et al teach a nucleic acid molecule having a polynucleotide sequence that encodes a protein having an amino acid sequence that is deemed the same as an antigenic epitope of SEQ ID NO:2 or a biologically active portion of SEQ ID NO:2, absent a showing of any differences. The Examiner stated further that the nucleic acid molecule taught by Joberty et al. comprises a nucleic acid sequence of SEQ ID NO:20.

In the absence of the specific reference supplied by the Examiner, applicants presume that the Examiner refers to the nucleic acid molecule and its encoded protein referenced by applicants as reference #20 of the IDS. The encoded protein, GenBank No. g8037915, is aligned with applicants SEQ ID NO:2 (Incyte ID 2582063) in Figures 3A-3J of the specification. It is clear from Figure 3B, in particular, that the nucleic acid molecule of Joberty et al. does not encode an antigenic epitope of SEQ ID NO:2 "from about amino acid residue K189 to about amino acid residue Q236 of SEQ ID NO:2". It further evident from Figures 3A-3J, and in particular Figure 3B, that the entire open reading frame of the Joberty sequence differs significantly from that of applicants sequence and therefore that the nucleic acid molecule of Joberty et al. does not anticipate, and therefore cannot "comprise" the nucleic acid sequence of SEQ ID

NO:20. Withdrawal of the rejection of claims 3 and 4 as anticipated by Joberty et al is therefore requested..

35 U.S.C. § 102(b), Rejection of Claims 3 and 4

The Examiner has rejected claims 3 and 4 under 35 U.S.C. § 102(b) as being anticipated by Izumi et al. (1998). The Examiner stated that Izumi et al teach a nucleic acid molecule having a polynucleotide sequence that encodes a protein having an amino acid sequence that is deemed the same as an antigenic epitope of SEQ ID NO:2 or a biologically active portion of SEQ ID NO:2, absent a showing of any differences. The Examiner stated further that the nucleic acid molecule taught by Izumi et al. comprises a nucleic acid sequence of SEQ ID NO:20.

The Izumi article cited by the Examiner is that of applicants reference #11 of the IDS. Page 98 of that article discloses the polypeptide recited in Figures 3A-3J of the instant application as Genbank No. g3868778. It is clear from Figure 3B, in particular, that the nucleic acid molecule of Izumi et al. does not encode and antigenic epitope of SEQ ID NO:2 "from about amino acid residue K189 to about amino acid residue Q236 of SEQ ID NO:2". It further evident from Figures 3A-3J, that the entire open reading frame of the Izumi sequence differs significantly from that of applicants sequence and therefore that the nucleic acid molecule of Izumi et al. does not anticipate, and therefore cannot "comprise" the nucleic acid sequence of SEQ ID NO:20. Withdrawal of the rejection of claims 3 and 4 as anticipated by Izumi et al is therefore requested..

35 U.S.C. § 102(b), Rejection of Claims 3 and 4

The Examiner has rejected claims 3 and 4 under 35 U.S.C. § 102(b) as being anticipated by NCBI-CGAP (Database Accession No. AI079538, 1998). The Examiner stated that NCBI-CGAP teaches a nucleic acid molecule having a polynucleotide sequence that encodes a protein having an amino acid sequence that is deemed the same as an antigenic epitope of SEQ ID NO:2 or a biologically active portion of SEQ ID NO:2, absent a showing of any differences. The Examiner stated further that the nucleic acid molecule taught by NCBI-CGAP comprises a nucleic acid sequence of SEQ ID NO:20; in fact the nucleic acid molecule comprises SEQ ID NO:21.

In the absence of a specific nucleic acid sequence provided by the Examiner, applicants have referenced the sequence defined by NCBI-CGAP Database Accession No. AI079538 from the NCBI database, and is attached as Exhibit B. Applicants have also provided a sequence alignment between the nucleic acid molecule, AI079538 and Incyte ID Nos. 2582063 (SEQ ID NO:20), and 2582063H1 (SEQ ID NO:21) of the Sequence Listing as Exhibit C, using the MEGALIGN program recited at p. 5, lines 23-24 of the specification.

It is readily apparent from this alignment that no contiguous nucleotide alignments of more that 8 nucleotides can be found throughout the alignment of AI0799538 with SEQ ID NO:20 or SEQ ID NO:21. It is therefore evident that the nucleic acid molecule taught by Accession No. AI079538 does not anticipate

an antigenic epitope of SEQ ID NO:2 from about amino acid residue K189 to about amino acid residue Q236 of SEQ ID NO:2, and furthermore does not anticipate, nor comprise, a polynucleotide sequence of SEQ ID NO:20 or SEQ ID NO:21. Withdrawal of the rejection of claims 3 and 4 as anticipated by Accession No. AI0799538 is therefore requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited. Applicants further request that, upon allowance of claims 1 and 5, that claims 9-14 be rejoined and examined as methods of use of the polynucleotides of claims 1 and 5 that depend from and are of the same scope as claims 1 and 5 in accordance with *In re Ochiai and Brouwer* and the MPEP § 1801.04.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Agent of Record, below

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

Respectfully submitted,
INCYTE GENOMICS, INC.

Date: February 24, 2003 David G. Streeter

David G. Streeter, Ph.D.
Reg. No. 43,168
Direct Dial Telephone: (650) 845-5741

3160 Porter Drive
Palo Alto, California 94304
Phone: (650) 855-0555
Fax: (650) 849-8886

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

Paragraph beginning at line 4 of page 31 has been amended as follows:

The BLAST software suite, freely available sequence comparison algorithms (NCBI, Bethesda MD[; http://www.ncbi.nlm.nih.gov/gorf/bl2.html]), includes various sequence analysis programs including "blastn" that is used to align nucleic acid molecules and BLAST 2 that is used for direct pairwise comparison of either nucleic or amino acid molecules. BLAST programs are commonly used with gap and other parameters set to default settings, e.g.: Matrix: BLOSUM62; Reward for match: 1; Penalty for mismatch: -2; Open Gap: 5 and Extension Gap: 2 penalties; Gap x drop-off: 50; Expect: 10; Word Size: 11; and Filter: on. Identity is measured over the entire length of a sequence or some smaller portion thereof. Brenner et al. (1998; Proc Natl Acad Sci 95:6073-6078, incorporated herein by reference) analyzed the BLAST for its ability to identify structural homologs by sequence identity and found 30% identity is a reliable threshold for sequence alignments of at least 150 residues and 40%, for alignments of at least 70 residues.

Paragraph beginning at line 31 of page 32 has been amended as follows:

Following assembly, templates were subjected to BLAST, motif, and other functional analyses and categorized in protein hierarchies using methods described in USSN 08/812,290 and USSN 08/811,758, both filed March 6, 1997; in USSN 08/947,845, filed October 9, 1997; and in USSN 09/034,807, filed March 4, 1998. Then templates were analyzed by translating each template in all three forward reading frames and searching each translation against the PFAM database of hidden Markov model-based protein families and domains using the HMMER software package (Washington University School of Medicine, St. Louis MO[; http://pfam.wustl.edu/]). The cDNA was further analyzed using MACDNASIS PRO software (Hitachi Software Engineering), and LASERGENE software (DNASTAR) and queried against public databases such as the GenBank rodent, mammalian, vertebrate, prokaryote, and eukaryote databases, SwissProt, BLOCKS, PRINTS, PFAM, and Prosite.

IN THE CLAIMS:

Claims 1, 3 and 4 have been amended as follows:

1. (Thrice Amended) An isolated cDNA, or the complement thereof, encoding a protein having the amino acid sequence of [SEQ ID NO:1 or] SEQ ID NO:2, or a naturally occurring variant of [SEQ ID NO:1 or] SEQ ID NO:2 having at least 95% amino acid identity to [SEQ ID NO:1 or] SEQ ID NO:2.

3. (Twice Amended) An isolated cDNA, or the complement thereof, encoding a protein having the amino acid sequence of SEQ ID NO:2, or an antigenic epitope of SEQ ID NO:2 from about amino acid residue K189 to about amino acid residue Q236 of SEQ ID NO:2[, or a biologically active portion of SEQ ID NO:2].

4. (Twice Amended) An isolated cDNA comprising a sequence selected from:

a) a nucleic acid sequence of [SEQ ID NO:3 or] SEQ ID NO:20 or the complement thereof;

b) [a fragment of SEQ ID NO:3 selected from SEQ ID NOs:4-11 or the complement thereof or] a fragment of SEQ ID NO:20 consisting of SEQ ID NO:21[selected from SEQ ID NOs:21-39] or the complement thereof; and

c) a naturally occurring variant of [SEQ ID NO:3 or] SEQ ID NO:20 having at least 90% sequence identity to [SEQ ID NO:3 or] SEQ ID NO:20.